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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,558	07/31/2006	Udi Damari	27367U	8968

20529 7590 03/30/2009

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
03/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,558	DAMARI ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment of 4/10/2006 has been received and entered into the application file. Claims 1-51 have been cancelled; claims 52-89 have been added as new. All claims have been considered on the merits.

Priority

Acknowledgement is made of the instant application being a national stage entry under 35 USC 371 of international application PCT/IL04/00929, filed 10/10/2004, which further claims priority under 35 USC 119(e) to US provisional applications 60/509,546, filed 10/9/2003, and 60/536,508, filed 1/15/2004.

Oath/Declaration

The oath or declaration received 7/31/2006 is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

Information Disclosure Statement

The listing of references **in the Search Report** is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending

U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Furthermore, the listing of references **in the specification** is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the preamble of claim 52, it is not clear what the 'corresponding viable cartilage' corresponds *to*, e.g. size/shape of the impaired cartilage, histocompatibility of the recipient, size/shape of an unrelated tissue, etc. Correction is required.

Furthermore, in claim 52, step (a) requires provision of a receptacle containing the corresponding viable cartilage *having shape and size compatible with the target site in the organ*, it is not clear if it is the receptacle or the cartilage which is to have a shape and size compatible with the target site. If it is the cartilage which is to have a shape and size compatible with the target site, then antecedent basis is lacking for "the corresponding viable cartilage having shape and size compatible with the target site in the organ", as the claim did not previously define the corresponding viable cartilage as having any particular size and shape. Also, please note "compatible with" is not equivalent to "corresponding [to]"; thus a viable cartilage corresponding in size and shape with the target site is *not* the same as a viable cartilage have a size and shape *compatible* with the target site.

Still further, in claim 52, step (b) requires cooling said corresponding viable cartilage to a temperature below said freezing temperature, however it is unclear if just the corresponding viable cartilage is frozen, or if both the cartilage and the cryopreservation solution. If just the cartilage is cooled, it is unclear if the freezing temperature referred to is that of the cartilage or of the cryopreservation solution?

Finally, claim 52 is directed to a method of providing a patient having impaired cartilage in an organ at a target site with a corresponding viable cartilage (i.e. a method of providing cartilage to a patient); however the body of claim 52 does not set forth any step of actually *providing* any cartilage to the patient, none of dependent claims 53-63 recite such a step either. Therefore, claims 52-63 are rejected as being indefinite because the steps of the method do not properly correlate with the preamble.

Claim 55 is further rejected because it is not clear if the now frozen cartilage (and presumably cryopreservation solution) is still present in the receptacle at the point of transfer, or if just the receptacle is transferred. It is noted that claim 52 recites as an end product "a frozen corresponding viable cartilage", not "a frozen corresponding viable cartilage in a receptacle", such need not be recited in claim 52, but it would be remedial to make it clear in claim 55 that the step involves transferring the receptacle *containing* the frozen corresponding viable cartilage to storage...

In claim 57, in step (e) it is unclear if the temperature that is "at least substantially equal to" the melting temperature of the solution may be higher or lower than the melting temperature of the solution. For example, should the claim read "... to a temperature that is at least substantially equal to *or greater than* the melting temperature of the solution..." or "... to a temperature that is at least substantially equal to *or less than* the melting temperature of the solution..." Because the claims refer to a variety of temperature changes, both positive and negative, it is unclear what is intended in the instant claim.

Claim 68, step (b) requires cooling the viable cartilage to a temperature below the freezing temperature, however it is unclear what freezing temperature is being referenced, the freezing temperature of the cartilage or the freezing temperature of the cryoprotectant solution? The same problem exists in claim 69.

In claim 70 the velocity of the movement along the temperature gradient fails to limit the rate at which the temperature is raised, because the temperature along any particular gradient pathway is not disclosed. Therefore it is unclear what claim 70 is adding to the invention.

Claim 73 is further rejected because it is not clear if the now frozen cartilage (and presumably cryopreservation solution) is still present in the receptacle at the point of transfer, or if just the receptacle is transferred. It is noted that claim 68 recites as an end product "a frozen viable cartilage", not "a frozen

viable cartilage in a receptacle", such need not be recited in claim 68, but it would be remedial to make it clear in claim 73 that the step involves transferring the receptacle *containing* the frozen viable cartilage to storage...

Claim 76 is rejected as lacking antecedent basis for the limitation "the frozen corresponding viable cartilage" in lines 3 and 12 of the claim, the preamble only refers to "frozen viable cartilage" not frozen corresponding viable cartilage. As discussed with reference to claim 52, it is unclear what the cartilage corresponds *to*, clarification is required if this term remains in the claim.

Furthermore, in claim 76 in step (b), it is unclear if "the glass transition temperature" is that of the solution in which the frozen cartilage is stored, or the glass transition temperature of the cartilage.

Claim 78 is further rejected as depending on a cancelled claim (claim 26). It appears claim 78 should depend from claim 76.

In the preamble of claim 87, it is not clear what the 'corresponding thawed viable cartilage' corresponds *to*, e.g. size/shape of the impaired cartilage, histocompatibility of the recipient, size/shape of an unrelated tissue, etc. Correction is required.

Furthermore, claim 87 references the 'corresponding thawed viable cartilage of claim 76' however claim 76 is directed to a method of thawing cartilage, not to the thawed cartilage per se. Perhaps claim 87 should refer to the thawed cartilage of claim *86*, which is made by the process of claim 76.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Though the preamble of claim 52 discloses a method of providing a patient with a corresponding viable cartilage, there are no recited steps of providing a patient with any cartilage; therefore, the preamble is not considered to impart any patentable weight on the claim.

Claims 52, 54-56, 68 and 72-75 are rejected under 35 U.S.C. 102(b) as being anticipated by Schachar et al (J Orthop Res, 1999), in light of Sigma Product Information Sheet for Dimethyl sulfoxide.

Schachar et al disclose freezing osteochondral dowels in a process comprising: immersing the osteochondral dowels in DMSO for 30 minutes at 20°C; then cooling the osteochondral dowels to -40°C at a controlled rate of -1°C/min; followed by storage at -80°C (See Schachar et al, Pg. 911, "Allografts"). Schachar et al further disclose the cryopreserved allografts thereby produced.

DMSO is used as the cryopreservation solution. DMSO has a melting point (which Applicants call the freezing temperature) of 18.45°C (See Sigma Product Info Sheet). Therefore, by initially providing the osteochondral dowels in DMSO at 20°C the osteochondral dowel was provided in a cryopreservation solution above the freezing temperature of the cryopreservation solution; subsequent cooling at a rate of -1°C/min to -40°C resulted in generation of a frozen osteochondral dowel at a temperature below the freezing temperature of the cryopreservation solution. Storage at -80°C was well below the freezing temperature of the cryopreservation solution.

Though Schachar et al do not explicitly disclose the osteochondral sample was provided 'in a receptacle', it will be readily understood by one of ordinary skill in the art that the sample was necessarily provided in some form of receptacle, as a receptacle is necessary to contain the liquid DMSO, as well as to contain the sample during the cooling procedure. Thus the method of Schachar et al is identical to that currently claimed, and the resulting frozen cartilage product is also anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52-56 and 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schachar et al (J Orthop Res, 1999), in light of Sigma Product Information Sheet for Dimethyl sulfoxide.

The teachings of Schachar et al are set forth above.

Schachar et al differ from claims 53 and 69-71 with regards to how the osteochondral sample is subjected to the cooling temperatures. Schachar et al cool the sample using a controllable freezing chamber, which does not appear to physically move the sample to areas of progressively lower temperatures, but rather lowers the temperature within the chamber at the set rate. However, it is submitted that the physical placement of the product within an environment of progressively lower temperatures does not patentably distinguish the method of cooling. Changing the temperature around a stationary sample versus physically moving the sample to environments of different temperatures produces the same effect, so long as the temperature change is at the same rate, therefore substitution of one method for the other, to yield the predictable result of cooling the osteochondral sample at a rate of -1°C/min to -40°C, would have been *prima facie* obvious to one of ordinary skill in the art.

Claims 52-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pegg et al (Cryobiology, 1997), in view of Schachar et al (J Orthop Res, 1999).

Pegg et al disclose immersing artery tissue in 20 mL of a cryoprotectant solution comprising DMSO in CPTES, followed by cooling at a rate of -1°C/min to -180°C, and followed by storage in the gas phase of liquid nitrogen (-180°C), to thereby create cryopreserved artery tissues (See Pegg et al, Pg. 187 "Experiment 3").

Pegg et al disclose rewarming the cryopreserved tissues in a two-step process reduced the number of fractures in the thawed tissues. The first step of the two-step process involved removing the cryopreserved samples from the liquid nitrogen refrigerator and placing them in an insulated outerbag at room temperature; during this stage the tissues were allowed to warm from -180°C to -100°C (at an initial rate of 40-60°C/min, slowing to 15-17°C/min as the temperature approached -100°C). The second step of the two-step process involved immersing the bagged samples in a warm water bath (37°C); during this stage the tissues were allowed to completely thaw (at an initial rate of over 2000°C/min, slowing to 50-80°C/min after 15 seconds). Pegg et al report this two-step warming process, when the sample is brought to a temperature of at least -120°C, preferably -100°C, during the first stage significantly reduced or eliminated fractures as compared with the conventional single-step warming process, involving immediate immersion in warm water (See Pegg et al, Pg. 187-188 "Experiment 4").

The method of Pegg et al does not anticipate the current claims because Pegg et al use artery segments, not cartilage. However, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art to apply the cryopreservation method of Pegg et al, involving the cryopreservation at a controlled rate, and the two-step rewarming process, to other types of tissues which are desired to be cryopreserved for future application, for the predictable result of reducing damaged associated with cryopreservation in the other tissue types.

At the time the invention was made there was a recognized need for an improved method of cryopreserving cartilage that resulted in increased cell survival; such an improved method would permit development and maintenance of supplies of available cartilage tissue for surgical transplantation (See Schachar et al, Pg. 909-910).

Schachar et al disclose cryopreserving osteochondral tissue samples, and subsequently thawing and implanting the thawed tissues into joint defects in recipients (See Schachar et al, Pg. 911-912 "Treatment Groups" and "Assessment of Cartilage"). Schachar et al report their cryopreservation method (including a single step rapid rewarming in a 37°C water bath) only results in 50% recovery of chondrocytes, and has widespread lethal injury to chondrocytes in the intermediate zone of the cartilage (See Schachar et al, paragraph spanning Pg. 916-917).

Therefore, it would have been obvious to one of ordinary skill in the art to apply the cryopreservation method of Pegg et al to osteochondral tissues that are to be cryopreserved and subsequently thawed for use in transplantation procedures, as taught by Schachar et al. Using the cryopreservation technique of Pegg et al, including the improved two-step warming process, to provide the benefit of reduced damage to the tissue associated with cryopreservation would have been obvious to one of ordinary skill. See *KSR International Co v Teleflex, Inc* 550 US--- 82 USPQ2d 1385 (2007).

Application of the cryopreservation method of Pegg et al, including both the actual cryopreservation to temperatures of -180°C, and subsequent thawing via a two-step rewarming process, to osteochondral tissues reads on the methods of claims 52, 54-58, 60-62, 65-68, 72-74, 76-78, 82-84 and 87-89, as well as the tissue product of claims 64, 75, 86.

It is noted the cryopreservation method of Pegg et al differs from the method of the current claims with respect to the method by which the sample is exposed to cooling temperatures; the exact warming rates of the first and second stages; and use of a pulling member to remove the tissue from the receptacle;

however, each of these differences would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and thus do not patentably distinguish over a method of subjecting osteochondral tissue to the cryopreservation method of Pegg et al, and subsequently transplanting the thawed tissue in reconstruction procedures.

Specifically, with regards to the method by which the sample is exposed to the cooling temperatures, it is submitted that the physical placement of the product within an environment of progressively lower temperatures does not patentably distinguish the method of cooling. Changing the temperature around a stationary sample versus physically moving the sample to environments of different temperatures produces the same effect, so long as the temperature change is at the same rate, therefore substitution of one method for the other, to yield the predictable result of cooling the osteochondral sample at a rate of -1°C/min to -180°C, would have been *prima facie* obvious to one of ordinary skill in the art.

With regards to the warming rates in the two stages, it is submitted that such temperatures would have been routinely optimized by the artisan of ordinary skill, Pegg et al sets forth the general conditions (i.e. a first step of slow-warming, followed by a second step of extremely rapid warming) suitable for the method, and it has been held that "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Finally, with regards to use of a 'pulling member' to remove the sample from the receptacle, it is submitted that any sterile means for recovery of a biological sample, such as cryopreserved and/or thawed cartilage from its holding receptacle, would have been *prima facie* obvious to the artisan of ordinary skill. Due to the extreme temperatures use of laboratory tools would have been recognized as necessary to permit safe (and sterile) recovery of the biological samples.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651